JACC Vol. 18, No. 4
October 1991:1077–84

REVIEWS

Limitations of Thrombolytic Therapy for Acute Myocardial Infarction Complicated by Congestive Heart Failure and Cardiogenic Shock

ERIC R. BATES, MD, FACC, ERIC J. TOPOL, MD, FACC

Ann Arbor, Michigan

As many as one quarter of patients treated with thrombolytic therapy present with congestive heart failure or cardiogenic shock. Although thrombolytic therapy has been shown to limit infarct size, preserve left ventricular ejection fraction and decrease mortality in most subgroups of patients, no apparent benefit has been demonstrated in patients with clinical left ventricular dysfunction. The lack of correlation between ejection fraction and other measurements of left ventricular dysfunction such as exercise time, cardiac output, filling pressures, activation of the neurohumoral system and regional perfusion bed abnormalities may partly explain this paradox. Alternatively, lower perfusion rates, higher reocclusion rates, associated mechanical complications or completed infarction may explain these findings.

Preliminary data indicate that emergency coronary angioplasty or bypass graft surgery improves survival in selected patients with cardiogenic shock. Because these findings suggest that restoration of infarct artery patency is especially important in patients with clinical left ventricular dysfunction, additional studies are needed in these patients to investigate the potential benefit that new thrombolytic strategies, inotropic or vasodilator agents or intraaortic balloon counterpulsation might offer by augmenting coronary blood flow and improving reperfusion rates. Currently, acute mechanical revascularization should be considered for patients who present with congestive heart failure associated with hypotension or tachycardia and for patients with cardiogenic shock.

(J Am Coll Cardiol 1991;18:1077–84)

Several controlled trials (1–5) of intravenous thrombolysis in acute myocardial infarction have verified the important lifesaving potential of this therapy. Although overall benefit has consistently been shown, certain subgroups of patients have had equivocal results. Whereas elderly patients demonstrate apparent mortality reduction from reperfusion therapy (1–4) and data are supportive for treating patients with late presentation (3,5), inferior myocardial infarction (2–4), hypertension (3), previous myocardial infarction (3,6), limited cardiopulmonary resuscitation (7) and new bundle branch block (3), patients with ST segment depression have not shown survival benefit (1,3). Until additional evidence suggests differently, most investigators (8,9) recommend withholding therapy in this subgroup, although others (10) suggest that the limitations of subset analysis explain the lack of benefit and thus all patients with presumed myocardial infarction should be treated.

Curiously missing from previous reports regarding subset analyses are the results of thrombolytic therapy in patients with congestive heart failure and cardiogenic shock. In this review, we summarize the available reperfusion trial data for this important subgroup of patients who present for treatment with left ventricular decompensation and recommend a management approach.

Congestive Heart Failure

Risk stratification. Killip and Kimball (11) initially described the progressive influence of congestive heart failure, pulmonary edema and cardiogenic shock on the incidence of death in 250 consecutive patients with myocardial infarction treated in a coronary care unit setting (Table 1). This scheme of risk stratification remains clinically useful today. In fact, two major thrombolytic trials (1,12,13) have used this classification in reporting results. Table 2 shows that almost 25% of patients enrolled in these trials had congestive heart failure (Killip class II) or pulmonary edema (Killip class III) at presentation. Unfortunately, it does not appear that a clinically important survival benefit was achieved with thrombolytic therapy (1) or thrombolytic therapy plus aspirin (12,13) compared with placebo (Table 3) or even with the initial experience of Killip and Kimball (Table 1) (11). The finding that 25% of patients in Killip class II and 50% of those in Killip class III were dead at 1 year in the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI-1) trial (14) (Table 3) is a sobering contrast to the excellent survival rates reported for treating relatively low risk patients in the Thrombolysis in Myocardial Infarction (TIMI)-II trial (15) and is somewhat surprising given the documented benefit of thrombolytic therapy in decreasing infarct size and preserving left ventricular ejection fraction.

From the Division of Cardiology, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan.

Manuscript received January 1, 1991; revised manuscript received April 8, 1991, accepted April 22, 1991.

Address for reprints: Eric Bates, MD, University of Michigan Medical Center, Department of Cardiology, B1-F245, Box 0022, Ann Arbor, Michigan 48109-0022.

0735-1097/91/$3.50

JACC Vol. 18, No. 4
October 1991:1077–84

Table 1. Hospital Mortality Rate According to Killip Class*

Killip Class	No. of Patients	Mortality Rate (%)
I (no CHF)	81 (33%)	6
II (CHF)	86 (38%)	17
III (pulmonary edema)	26 (10%)	38
IV (shock)	47 (19%)	81

*Data are from Killip and Kimball (11). CHF = congestive heart failure.

Infarct size. In a dog model, Reimer et al. (16) demonstrated that myocardial necrosis occurs over several hours after arterial occlusion, spreading in a wave front from endocardium to epicardium, and that reperfusion within 3 h could abort the process and preserve an epicardial rim of viable tissue. Using release of the enzyme hydroxybutyric dehydrogenase as a measure of infarct size, Simoons et al. (17) reported a remarkably similar result in humans, observing that intracoronary streptokinase reduced infarct size compared with that achieved with placebo when treatment was given within 3 h. Although, in humans, the time of total arterial occlusion can be difficult to determine, intermittent patency can occur and collateral circulation should preserve cell viability, no reduction in infarct size was seen in patients with >3 h of symptoms (17). A reduction in enzyme release in treated patients was also shown in the Intravenous Streptokinase in Acute Myocardial Infarction (ISAM) trial (18) and the fifth European Cooperative Study Group trial (19). However, no change in infarct size as measured by a nuclear imaging technique was found in treated patients in the Western Washington intracoronary streptokinase trial (20), where time to treatment averaged 4.7 h. The importance of decreasing infarct size by early reperfusion is illustrated by the fact that the greatest reduction in mortality occurs in patients treated within 1 h of symptom onset (1,3). Also, patients with the largest ischemic areas, the patients most likely to develop congestive heart failure, appear to have the greatest reduction in infarct size with treatment (21,22).

Left ventricular ejection fraction. Left ventricular ejection fraction is a strong predictor of death in patients with coronary artery disease (23). Whereas it was expected that a reduction in infarct size with thrombolytic therapy could preserve acute left ventricular ejection fraction and thus reduce mortality, it was surprising to find that late (24) or even delayed spontaneous (25) reperfusion in untreated patients could also improve ejection fraction and that late treatment could decrease mortality (3). Thus, it appears that arterial patency has a beneficial effect on left ventricular ejection fraction and mortality independent from myocardial salvage (26). It has been suggested (26) that restoration of coronary blood flow improves healing and decreases infarct expansion and left ventricular dilation after myocardial infarction. The reduction in end-systolic volume (27), mural thrombus formation and electrical instability (28) associated with arterial patency is a possible explanation for improved survival in patients without infarct size reduction.

The importance of successful thrombolysis in decreasing mortality in patients with a reduced ejection fraction was first shown in the Western Washington intracoronary streptokinase trial (29,30) (Fig. 1). Additionally, the greatest recovery of ejection fraction percentage points due to early thrombolysis has been found in patients with the lowest entry ejection fraction, the patients most likely to develop congestive heart failure, with little improvement possible in patients with a normal ejection fraction (31). The reported relatively small difference in mean ejection fraction between treated and control patients (5 to 8 percentage points) partly reflects the fact that 70% to 80% of patients with myocardial infarction and ST segment elevation have not previously had myocardial infarction (1–3), 66% may have one-vessel disease (32) and average left ventricular ejection fraction in survivors is 50% to 55% (33).

Thrombolytic therapy. Congestive heart failure is a clinical syndrome that is variably defined by physical signs, radiographic findings or medication profiles and therefore may be more difficult to accurately measure than infarct size or left ventricular ejection fraction. The distribution of Killip class at entry in the two large trials (1,12,13) with equivalent entry criteria (Table 2) was similar, with a slightly lower incidence of patients in Killip classes II to IV in the International trial (12,13) probably reflecting a shorter treatment window (6 h) than was used in GISSI-1 (12 h) (1). It is important when interpreting published findings to determine whether Killip class was documented at presentation to the hospital or whether it was noted during the course of hospitalization after treatment. Results from several trials

Table 2. Killip Class at Entry in Two Trials

	Killip I	Killip II	Killip III	Killip IV
GISSI-1 (1)				
SK	4,171 [71.2]	1,322 [22.7]	191 [3.2]	146 [2.5]
Placebo	4,105 [70.1]	1,340 [22.9]	246 [4.2]	134 [2.3]
International trial (12,13)				
SK/aspirin	8,247 [79.4]	1,634 [16.2]	284 [2.7]	175 [1.7]
rt-PA/aspirin	8,228 [79.3]	1,748 [16.9]	246 [2.4]	148 [1.4]

Data represent patient numbers. Numbers in brackets represent percents. GISSI-1 = Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico—I trial; rt-PA = recombinant tissue-type plasminogen activator; SK = streptokinase.

Table 3. Mortality Rates by Killip Class at Entry in Two Trials

	Killip I	Killip II	Killip III	Killip IV
Hospital mortality rate (%)				
GISSI-1 (1)				
SK	5.9*	16.1†	33	69.9
Placebo	7.3	19.9	39	70.1
International trial (12,13)				
SK/aspirin	5.1	17.8	33.3	64.9
rt-PA/aspirin	4.1	17.7	29.9	78.1
1-year mortality rate (%)				
GISSI-1 (14)				
SK	10.6†	26.6	50.3	76.6
Placebo	11.9	28.9	53.3	72.4

*p = 0.01; †p = 0.04. Abbreviations as in Table 2.

(4,6,17,34–38) show the incidence of congestive heart failure during the hospital course to vary widely (Table 4). Sample size, referral bias, entry criteria or thoroughness of data collection may explain some of the differences. Although not consistently found, there appears to be a lower incidence of congestive heart failure during hospitalization in treated compared with control patients (Table 4). Thus, whereas thrombolytic therapy may not dramatically decrease the high mortality rate in patients who present with congestive heart failure (Table 3), it may decrease the later development of congestive heart failure in patients who undergo successful reperfusion.

The potential ability of thrombolytic therapy to improve survival in patients with a low ejection fraction compared with poor results in those with congestive heart failure should not seem too perplexing. Previous studies (39,40) have demonstrated that ejection fraction is not related to other measurements of left ventricular function, such as exercise time, cardiac output and filling pressure. Moreover, the clinical syndrome of congestive heart failure is a complex multisystem disorder that can involve abnormalities of the neurohumoral system and regional perfusion beds. The failure of thrombolytic therapy to dramatically decrease mortality in patients who present with congestive heart failure could be explained by physiologically more significant left ventricular dysfunction, lower reperfusion rates, associated mechanical complications (mitral regurgitation, ventricular septal defect, myocardial rupture) or completed infarction. Baseline left ventricular ejection fraction before myocardial infarction may not be critically related because survival benefit was shown in treated patients with prior myocardial infarction in both the ISIS-2 (3) and APSAC Intervention Mortality Study (AIMS) (6) trials.

Left ventricular ejection fraction: mortality paradox. Van de Werf (41) noted that although placebo-controlled trials have demonstrated either significant improvement in left ventricular ejection fraction or significant reduction in mortality, no single study has shown improvement in both end points. This is paradoxic because the greatest mortality benefit from thrombolysis would be expected in patients with a larger infarct size and lower ejection fraction. It was postulated that early thrombolytic therapy in patients with large areas of injured myocardium and severe left ventricular dysfunction might improve survival, leading to a lower mean ejection fraction in treated patients compared with control patients; in the latter group, mean ejection fraction might conversely be increased by the death of high risk patients with poor ventricular function before the ejection fraction measurement could be determined (41). The validity of this hypothesis, however, depends on the lack of correlation between left ventricular ejection fraction and congestive heart failure, because it does not appear that thrombolytic therapy dramatically alters the incidence of death in patients who present with congestive heart failure or pulmonary edema.

Other investigators (33,42) have questioned whether ejection fraction should even be considered a valid end point in comparative trials. First, the measurement may be missing from as many as 30% of patients enrolled in a trial because of deaths and unobtained or technically inadequate studies

Figure 1. Relation between left ventricular ejection fraction at admission and 1-year survival rates in the Western Washington intracoronary streptokinase trial (29) by treatment strategy and reperfusion status. Reproduced from Stadius (30), with permission. Rx = treatment.

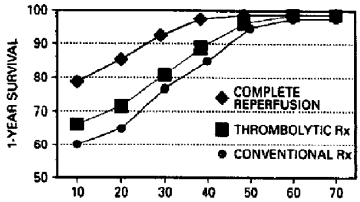

Table 4. Incidence of Congestive Heart Failure During Hospitalization

Study	Thrombolysis	Placebo
ASSET (4)	446/2,512 [17.7]	461/2,493 [18.4]
Guerci et al. (34)	10/72 [14]	22/66 [23]
NHF (35)	20/73 [27.4]	26/71 [36.6]
Simoons et al. (17)	37/269 [13.8]	53/264 [20.1]
Meinertz et al. (36)	32/162 [20]	43/151 [29]
Bassand et al. (37)	8/112 [6.7]	15/119 [13.4]
Follow-up		
ISAM (38) (7 mo)	58/859 [6.6]	80/882 [9.1]
AIMS (6) (1 yr)	131/624 [21]	154/634 [24]

Data represent patient numbers. Numbers in brackets represent percents. AIMS = APSAC Intervention Mortality Study; ASSET = Anglo-Scandinavian Study of Early Thrombolysis; ISAM = Intravenous Streptokinase in Acute Myocardial Infarction Trial; NHF = National Heart Foundation of Australia Coronary Thrombolysis Trial.

(33). Second, there is no correlation between preservation of left ventricular ejection fraction and time to treatment (33). Third, compensatory noninfarct zone hyperkinesia can maintain ejection fraction and mask treatment benefit (43). Finally, left ventricular ejection fraction is significantly dependent on ventricular loading conditions that may change during the course of acute myocardial infarction (42).

Cardiogenic Shock

Incidence. Cardiogenic shock remains the leading cause of death after hospitalization for acute myocardial infarction (44). It has been suggested that the incidence of cardiogenic shock has declined in recent years, partly as a result of earlier hospitalization and the use of thrombolytic agents (44). Equally likely, however, are the possibilities that early reports from tertiary care referral centers overestimated the incidence of cardiogenic shock compared with admission rates in community hospitals and that hypovolemic shock was underdiagnosed before central hemodynamic monitoring became possible (45). Data from the Multicenter Investigation of Limitation of Infarct Size (MILIS) Study Group (46) obtained in the 1970s demonstrated that 4.5% of patients with acute myocardial infarction presented with cardiogenic shock (44) and that 7.1% developed cardiogenic shock after hospital admission. In GISSI-1 (1), a community hospital trial, 2.5% of patients presented with cardiogenic shock and 6% developed shock during hospitalization. Mortality rates are influenced by the length of the observation period and have been reported (1,11–13,46) to range from 65% to 80%.

Cardiogenic shock develops when >40% of the left ventricle becomes dysfunctional because of ischemia or infarction (47). Coronary care unit monitoring, pharmacologic treatment with vasopressor agents, vasodilators and inotropic agents and intraaortic balloon counterpulsation have not significantly altered mortality rates (48). More recent attempts at improving survival have involved reperfusing ischemic myocardium with thrombolytic therapy, coronary angioplasty or coronary bypass graft surgery.

Thrombolytic therapy. Mathey et al. (49,50) were the first to report successful reperfusion with intracoronary streptokinase and survival in three patients with cardiogenic shock. Forty-four patients were similarly treated in the Society for Cardiac Angiography's intracoronary streptokinase registry (51). In 44 patients, the overall mortality rate was 66%, but patency was achieved in only 44%. In the 19 patients with successful reperfusion, the mortality rate was 42%; in 25 patients in whom reperfusion was unsuccessful, the mortality rate was 84%. The low patency rate in this subset contrasts sharply with the overall patency rate of 71% in the registry. The low output state associated with cardiogenic shock may explain this finding. Recent work in an animal model of pulmonary embolism (52) emphasizes the importance of cardiac output on successful thrombolysis. Increasing a low cardiac output by 50% improved the patency rate by 50%.

Equivalent mortality rates to those reported in the Society for Cardiac Angiography's intracoronary streptokinase registry were found with intravenous streptokinase in GISSI-1 (1) and the International trial (12,13) (Table 3), but the mortality rate did not differ from that in the placebo-treated patients in GISSI-1 (1) or patients enrolled in the MILIS study (46). The MILIS study (46) additionally showed that infarct extension occurred in 23% of patients with cardiogenic shock compared with 7% of those without shock. The higher mortality rate in patients with cardiogenic shock treated with recombinant tissue-type plasminogen activator (rt-PA) in the International trial (12,13) may reflect the higher reocclusion rates that can occur when intravenous heparin is not used with rt-PA (53). Furthermore, after thrombolytic therapy the incidence of cardiogenic shock during hospitalization increases to 4% to 6% (1,54), similar to the rate reported in the MILIS trial (46). From available data, it is not clear that thrombolytic therapy has reduced mortality due to cardiogenic shock.

Mechanical revascularization in cardiogenic shock. At least 14 reports (48,55–67)* exist regarding the use of emergency coronary angioplasty in patients with cardiogenic shock (Table 5). These show a reduction in mortality from the 65% to 80% reported in previous studies (1,11–13,46) to 44%. Patency rates are 30 percentage points higher than those seen with intracoronary thrombolytic therapy (51). Successful reperfusion in this meta-analysis was associated with a 30% mortality rate, whereas that after unsuccessful reperfusion was similar to that of historical control subjects. Interestingly, mortality rates associated with success or failure of reperfusion are similar to those reported for the Society for Cardiac Angiography's intracoronary streptokinase registry (51). This finding lends further support to the concept that immediate reduction of a residual coronary stenosis by coronary angioplasty provides no additional benefit to restoration of coronary blood flow in patients with acute myocardial infarction (68–70). Patency rates after emergency angioplasty for acute myocardial infarction are somewhat lower than those reported for elective angioplasty in patients with angina pectoris (71) and success rates in patients with cardiogenic shock are also lower than those noted in other patients with acute myocardial infarction (72).

Emergency bypass graft surgery has been used infrequently in patients with cardiogenic shock (73–86) but with good results since 1980 (Table 6), although selection bias may have influenced outcome. Success is probably more dependent on the skill of the surgical team than is the case with coronary angioplasty, where results tend to be more consistent among centers. Other benefits of coronary angioplasty compared with bypass graft surgery, besides lower cost, are due to the speed and efficiency with which angioplasty can be initiated. Access to the catheterization laboratory is easier and quicker than to the surgical suite, reperfu-

*Five of these reports are abstracts published from 1985 to 1988.

Table 5. Coronary Angioplasty for Cardiogenic Shock Complicating Acute Myocardial Infarction

Study	No.	Reperfusion Rate	Mortality Rate		
			Total	+Reperfusion	−Reperfusion
O'Neill et al. (55)	27	24/27 [88]	8/27 [30]	6/24 [25]	2/3 [67]
Shani et al. (56)	9	6/9 [67]	3/9 [33]	N/A N/A	N/A N/A
Heuser et al. (57)	10	6/10 [60]	4/10 [30]	1/6 [17]	3/4 [75]
Brown et al. (58)	28	17/28 [61]	16/28 [57]	7/17 [42]	9/11 [82]
Laramee et al. (59)	39	33/39 [86]	16/39 [41]	N/A N/A	N/A N/A
Lee et al. (48)	24	13/24 [54]	12/24 [50]	3/13 [23]	9/11 [82]
Lee et al. (60)	69	49/69 [71]	31/69 [45]	15/49 [31]	16/20 [80]
Gacioch and Topol (61)	25	18/25 [72]	11/25 [44]	4/18 [22]	7/7 [100]
Disler et al. (62)	7	5/7 [71]	4/7 [57]	2/5 [40]	2/2 [100]
Verna et al. (63)	7	7/7 [100]	1/7 [14]	1/7 [14]	0/0 [0]
Meyer et al. (64)	25	22/25 [88]	12/25 [47]	9/22 [41]	3/3 [100]
Hibbard et al. (65)	45	28/45 [62]	20/45 [44]	8/28 [29]	12/17 [71]
Moosvi et al. (66)	38	29/38 [76]	18/38 [47]	11/29 [38]	7/9 [78]
Elchaninoff et al. (67)	33	25/33 [76]	12/33 [36]	6/25 [24]	6/8 [75]
Total	386	282/386 [73]	168/386 [44]	73/243 [30]	76/95 [80]

Data represent patient numbers. Numbers in brackets represent percents. N/A = not available; + = with; − = without.

sion can be achieved more rapidly and patients with multiorgan hypoperfusion or advanced age may have lower risk than with surgery. The use of percutaneous support devices such as the intraaortic balloon pump (87), femoral-femoral bypass (88), coronary sinus retroperfusion (89) or the hemopump (90) potentially could maintain organ perfusion and limit organ damage during the reperfusion attempt in the catheterization laboratory.

Conclusions

Several conclusions can be drawn from existing data. First, early thrombolytic therapy can reduce infarct size and preserve left ventricular ejection fraction, but left ventricular ejection fraction can improve without infarct size reduction or early treatment if patency of the infarct-related artery is achieved (33). Second, preservation of left ventricular ejection fraction should decrease mortality risk, but mortality reduction can occur in the absence of improvement in left ventricular ejection fraction if patency of the infarct-related artery is achieved (41). Third, whereas thrombolytic therapy may decrease the incidence of heart failure complicating acute myocardial infarction, it does not clearly decrease mortality in patients who present with heart failure or cardiogenic shock. Finally, it is possible that mechanical reperfusion may significantly decrease mortality in patients with cardiogenic shock, but more data are needed.

Table 6. Coronary Artery Bypass Graft Surgery for Cardiogenic Shock Complicating Acute Myocardial Infarction

Study (reference)	Year	No.	Mortality
Sandith et al. (73)	1973	33	20 [61]
Meier et al. (74)	1974	12	7 [58]
Willerson et al. (75)	1975	3	2 [67]
Johnson et al. (76)	1977	5	3 [60]
Ehrich et al. (77)	1977	3	2 [67]
Bardet et al. (78)	1977	4	2 [50]
O'Rourke et al. (79)	1979	6	4 [67]
Subramanian et al. (80)	1980	20	9 [45]
Merav et al. (80)	1980	7	2 [29]
DeWood et al. (81)	1980	19	8 [42]
Kirklin et al. (82)	1985	4	0 [0]
Phillips et al. (83)	1986	34	8 [24]
Laks et al. (84)	1986	50	15 [30]
Guyton et al. (85)	1987	9	2 [22]
Bolooki (86)	1989	7	3 [43]
Total		216	87 [40]

Data represent patient numbers. Numbers in brackets represent percents.

Role of achieving coronary artery patency. It is likely that all of the therapeutic benefit associated with reperfusion therapy is the result of achieving patency of the infarct-related artery. Restoration of patency appears crucial for survival in patients with cardiogenic shock. Because thrombolytic therapy is associated with low patency rates and no survival benefit in patients in Killip class IV, it is interesting to speculate whether low patency rates or high reocclusion rates in patients in Killip classes II and III might be responsible for the discouraging survival rates seen with thrombolytic therapy. Because up to 25% of patients eligible for reperfusion therapy are in Killip classes II to IV, it will be critically important to determine in prospective trials whether higher patency rates associated with coronary angioplasty or front-loaded thrombolytic therapy (91) or lower reocclusion rates associated with combination thrombolytic therapy (92,93) can reduce the high mortality rates of patients who present with left ventricular decompensation despite standard thrombolytic therapy.

Recommendations. Until such data are forthcoming, every effort should be made to maximize patency of the infarct-related artery in these patients. Adjunctive therapy with aspirin (3) and intravenous heparin (33) should be

mandatory. Likewise, strong consideration should be given to augmenting coronary blood flow with inotropic or vasodilator agents (52) or with the intraaortic balloon pump (87) to improve reperfusion rates. Finally, mechanical revascularization should be considered for patients with cardiogenic shock or congestive heart failure associated with hypotension or tachycardia.

References

1. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986;1:397–401.
2. AIMS Trial Study Group. Effect of intravenous APSAC on mortality after acute myocardial infarction: preliminary report of a placebo-controlled clinical trial. Lancet 1988;1:545–9.
3. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988;2:349–60.
4. Wilcox RG, von der Lippe G, Olsson CG, Jensen G, Skene AM, Hampton JR for the ASSET Study Group. Trial of tissue plasminogen activator for mortality reduction in acute myocardial infarction. Lancet 1988;2:525–30.
5. Yusuf S, Collins R, Peto R, et al. Intravenous and intracoronary fibrinolytic therapy in acute myocardial infarction: overview of results on mortality, reinfarction and side-effects from 33 randomized controlled trials. Eur Heart J 1985;6:556–85.
6. AIMS Trial Study Group. Long-term effects of intravenous anistreplase in acute myocardial infarction: final report of the AIMS study. Lancet 1990;335:427–31.
7. Tenaglia AN, Califf RM, Candella RJ, et al. Thrombolytic therapy in patients requiring cardiopulmonary resuscitation. Am J Cardiol 1990 (in press).
8. Guerci AD. Unresolved issues: treatment of elderly patients and patients with inferior infarction and non-ST-segment infarcts. Coronary Artery Dis 1990;1:34–8.
9. Grines CL, DeMaria AN. Optimal utilization of thrombolytic therapy for acute myocardial infarction: concepts and controversies. J Am Coll Cardiol 1990;16:223–31.
10. Yusuf S, Sleight P, Held P, McMahon S. Routine medical management of acute myocardial infarction: lessons from overviews of recent randomized controlled trials. Circulation 1990;82(suppl II):II-117–34.
11. Killip T, Kimball JT. Treatment of myocardial infarction in a coronary care unit: a two-year experience with 250 patients. Am J Cardiol 1967; 20:457–64.
12. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-2: a factorial randomized trial of alteplase versus streptokinase and heparin versus no heparin among 12,490 patients with acute myocardial infarction. Lancet 1990;336:65–71.
13. The International Study Group. In-hospital mortality and clinical course of 20,891 patients with suspected acute myocardial infarction randomized between alteplase and streptokinase with or without heparin. Lancet 1990;336:71–5.
14. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Long-term effects of intravenous thrombolysis in acute myocardial infarction: final report of the GISSI study. Lancet 1987;2:871–4.
15. Williams DO, Braunwald E, Knatterud G, et al. The Thrombolysis in Myocardial Infarction (TIMI) trial: outcome at one year of patients randomized to either invasive or conservative management (abstr). Circulation 1989;80(suppl II):II-519.
16. Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon of ischemic cell death: 1. Myocardial infarct size versus duration of coronary occlusion in dogs. Circulation 1977;56:786–94.
17. Simoons ML, Serruys PW, van den Brand M, et al. Early thrombolysis in acute myocardial infarction: limitation of infarct size and improved survival. J Am Coll Cardiol 1986;7:717–28.
18. The I.S.A.M. Study Group. A prospective trial of intravenous streptokinase in acute myocardial infarction (I.S.A.M.): mortality, morbidity, and infarct size at 21 days. N Engl J Med 1986;314:1465–71.
19. Van de Werf F, Arnold AER. Intravenous tissue plasminogen activator and size of infarct, left ventricular function, and survival in acute myocardial infarction. Br Med J 1988;297:1374–9.
20. Ritchie JL, Davis KB, Williams DL, Caldwell J, Kennedy JW. Global and regional left ventricular function and tomographic radionuclide perfusion: the Western Washington intracoronary streptokinase in myocardial infarction trial. Circulation 1984;70:867–75.
21. Bar FW, Vermeer F, deZwaan C, et al. Admission electrocardiogram in predicting outcome of thrombolytic therapy in acute myocardial infarction. Am J Cardiol 1987;59:6–13.
22. Willems JL, Willems RJ, Willems GM, et al. Significance of initial ST segment elevation and depression for the management of thrombolytic therapy in acute myocardial infarction. Circulation 1990;82:1147–58.
23. The Multicenter Post-infarction Research Group. Risk stratification and survival after myocardial infarction. N Engl J Med 1983;309:331–6.
24. Schroder R, Neuhaus KL, Linderer T, Brugeman T, Tebbe U, Wagscheider K. Impact of late coronary artery reperfusion on left ventricular function one month after acute myocardial infarction (results from the ISAM study). Am J Cardiol 1989;64:878–84.
25. DeFeyter PJ, van Eenige MF, van der Wall EE, et al. Effects of spontaneous and streptokinase-induced recanalization on left ventricular function after myocardial infarction. Circulation 1983;67:1039–44.
26. Califf RM, Topol EJ, Gersh BJ. From myocardial salvage to patient salvage in acute myocardial infarction: the role of reperfusion therapy. J Am Coll Cardiol 1989;14:1382–8.
27. White HD, Norris RM, Brown MA, Brandt PWT, Whitlock RML, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. Circulation 1987;76: 44–51.
28. Kerrschot IE, Brugada P, Ramentol M, et al. Effects of early reperfusion in acute myocardial infarction on arrhythmias induced by programmed stimulation: a prospective, randomized study. J Am Coll Cardiol 1986;7: 1234–42.
29. Stadius ML, Davis K, Maynard C, Ritchie JL, Kennedy JW. Risk stratification for 1 year survival based on characteristics identified in the early hours of acute myocardial infarction: the Western Washington intracoronary streptokinase trial. Circulation 1986;74:703–11.
30. Stadius ML. After thrombolytic therapy: angiography, angioplasty, or surgery? Texas Heart Inst J 1990;17:165–72.
31. Sheehan FH. Determinants of improved left ventricular function after thrombolytic therapy in acute myocardial infarction. J Am Coll Cardiol 1987;9:937–44.
32. Topol EJ, Holmes DR, Rogers WJ. Coronary angioplasty after thrombolytic therapy for acute myocardial infarction. Ann Intern Med 1991; 114:877–85.
33. Califf RM, Harrelson-Woodlief L, Topol EJ. Left ventricular ejection fraction may not be useful as an end point of thrombolytic therapy comparative trials. Circulation 1990;82:1847–53.
34. Guerci AD, Gerstenblith G, Brinker JA, et al. A randomized trial of intravenous tissue plasminogen activator for acute myocardial infarction with subsequent randomization to elective coronary angioplasty. N Engl J Med 1987;317:1613–8.
35. National Heart Foundation of Australia Coronary Thrombolysis Group. Coronary thrombolysis and myocardial salvage by tissue plasminogen activator given up to 4 hours after onset of myocardial infarction. Lancet 1988;1:203–8.
36. Meinertz T, Kasper W, Schumacher M, Just H. The German multicentre trial of APSAC versus heparin for acute myocardial infarction. Am J Cardiol 1988;62:347–51.
37. Bassand J-P, Machecourt J, Cassagnes J, et al. for the APSIM Study Investigators. Multicenter trial of intravenous anisoylated plasminogen streptokinase activator complex (APSAC) in acute myocardial infarction: effects on infarct size and left ventricular function. J Am Coll Cardiol 1989;13:988–97.
38. Schröder R, Neuhaus K-L, Leizorovicz A, Linderer T, Tebbe U for the ISAM Study Group. A prospective placebo-controlled double-blind multicenter trial of intravenous streptokinase in acute myocardial infarction (ISAM): long-term mortality and morbidity. J Am Coll Cardiol 1987;9: 197–203.
39. Francioso JA. Functional capacity of patients with chronic left ventricular failure: relationship of bicycle exercise performance to clinical and hemodynamic characterization. Am J Med 1979;67:460–6.

40. Francioso JA, Park M, Levine TB. Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. Am J Cardiol 1981;47:33–9.
41. Van de Werf F. Discrepancies between the effects of coronary reperfusion on survival and left ventricular function. Lancet 1989;1:1367–8.
42. Wackers FJT. Thrombolytic therapy for myocardial infarction: assessment of efficacy by myocardial perfusion imaging with technetium-99m sestamibi. Am J Cardiol 1990;66:36E–41E.
43. Grines CL, Topol EJ, Califf RM, et al. Predictors of enhanced regional wall motion of the non-infarct zone after thrombolysis and angioplasty therapy of acute myocardial infarction. Circulation 1989;80:245–53.
44. Killip T. Cardiogenic shock complicating myocardial infarction. J Am Coll Cardiol 1989;14:47–9.
45. Swan HJC, Ganz W, Forrester J, Marcus H, Diamond G, Chonette D. Catheterization of the heart in man with use of a flow directed balloon-tipped catheter. N Engl J Med 1970;283:447–51.
46. Hands ME, Rutherford JD, Muller JE, et al, and the MILIS Study Group. The in-hospital development of cardiogenic shock after myocardial infarction: incidence, predictors of occurrence, outcome and prognostic factors. J Am Coll Cardiol 1989;14:40–6.
47. Alonso DR, Scheidt S, Post M, Killip T. Pathophysiology of cardiogenic shock: quantification of myocardial necrosis, clinical pathologic and electrocardiographic correlation. Circulation 1973;48:588–96.
48. Lee L, Bates ER, Pitt B, Walton JA, Laufer N, O'Neill WW. Percutaneous transluminal coronary angioplasty improves survival in acute myocardial infarction complicated by cardiogenic shock. Circulation 1988;78:1345–51.
49. Mathey D, Kuck KH, Remmecke J, Tilsner V, Bleifeld W. Transluminal recanalization of coronary artery thrombosis: a preliminary report of its application in cardiogenic shock. Eur Heart J 1980;1:207–12.
50. Mathey D, Kuck KH, Tilsner V, Krebber HJ, Bleifeld W. Nonsurgical coronary artery recanalization in acute transmural myocardial infarction. Circulation 1981;63:489–97.
51. Kennedy JW, Gensini GG, Timmis GC, Maynard C. Acute myocardial infarction treated with intracoronary streptokinase: a report of the Society for Cardiac Angiography. Am J Cardiol 1985;55:871–7.
52. Prewitt RM, Dounes AMT, Gu S, Chan SM, Dueas J. Effects of hydralazine and increased cardiac output on recombinant tissue plasminogen activator induced thrombolysis in canine pulmonary embolism. Chest 1991;99:708–14.
53. Hsia J, Hamilton WP, Kleiman N, Roberts R, Chaitman BR, Ross AM. A comparison between heparin and low-dose aspirin as adjunctive therapy with tissue plasminogen activator for acute myocardial infarction. N Engl J Med 1990;323:1433–7.
54. Garrahy PJ, Henzlova MJ, Forman S, Rogers WJ. Has thrombolytic therapy improved survival from cardiogenic shock? Thrombolysis in Myocardial Infarction (TIMI II) results (abstr). Circulation 1989;80(suppl II):II-623.
55. O'Neill WW, Erbel R, Laufer N, et al. Coronary angioplasty therapy of cardiogenic shock complicating acute myocardial infarction (abstr). Circulation 1985;72(suppl III):III-309.
56. Shani J, Rivera M, Geengart A, Hollander G, Kaplan P, Lichstein E. Percutaneous transluminal coronary angioplasty in cardiogenic shock (abstr). J Am Coll Cardiol 1986;7:149A.
57. Heuser RR, Maddoux GL, Goss JE, Ramo BW, Raff GL, Shadoff N. Coronary angioplasty in the treatment of cardiogenic shock: the therapy of choice (abstr). J Am Coll Cardiol 1986;7:219A.
58. Brown TM, Iannone LA, Gordon DF, et al. Percutaneous myocardial reperfusion reduces mortality in acute myocardial infarction complicated by cardiogenic shock (abstr). Circulation 1985;72(suppl III):III-309.
59. Larumee LA, Rutherford BD, Ligon RW, McConahay DR, Hartzler GO. Coronary angioplasty for cardiogenic shock following myocardial infarction (abstr). Circulation 1988;78(suppl II):II-634.
60. Lee L, Erbel R, Brown TM, Laufer N, Meyer J, O'Neill WW. Multicenter registry of angioplasty therapy of cardiogenic shock: initial and long term survival. J Am Coll Cardiol 1991;17:599–603.
61. Gacioch GM, Topol EJ. Frontiers in cardiogenic shock management: integration of angioplasty and new support devices (abstr). Circulation 1989;80(suppl II):II-624.
62. Disler L, Haitas B, Benjamin J, Steingo L, McKibbon J. Cardiogenic shock in evolving myocardial infarction: treatment by angioplasty and streptokinase. Heart Lung 1987;16:649–52.
63. Verma E, Repetto S, Boscarini M, Ghezzi L, Binaghi G. Emergency coronary angioplasty in patients with severe left ventricular dysfunction or cardiogenic shock after acute myocardial infarction. Eur Heart J 1988;10:958–66.
64. Meyer P, Blanc P, Pudouy M, Morand P. Treatment de choc cardiogenique primaire par angioplastie transluminale coronarienne a la phase aigue de l'infarctus. Arch Mal Coeur 1990;83:329–34.
65. Hibbard MD, Holmes DR, Gersh BJ, Reeder GS. Coronary angioplasty for acute myocardial infarction complicated by cardiogenic shock (abstr). Circulation 1990;82(suppl III):III-511.
66. Moosvi AR, Villanueva L, Gheorghiade M, Khaja F, Goldstein S. Early revascularization improves survival in cardiogenic shock (abstr). Circulation 1990;82(suppl III):III-308.
67. Eltchaninoff H, Simpfendorfer C, Whitlow PL. Coronary angioplasty improves both early and 1 year survival in acute myocardial infarction complicated by cardiogenic shock (abstr). J Am Cardiol Coll 1991;17:167A.
68. Topol EJ, Califf RM, George BS, et al. A randomized trial of immediate vs. delayed selective angioplasty after intravenous tissue plasminogen activator in acute myocardial infarction. N Engl J Med 1987;317:581–8.
69. Simoons ML, Arnold AER, Betriu A, et al. Thrombolysis with tissue plasminogen activator in acute myocardial infarction: no additional benefit from immediate percutaneous coronary angioplasty. Lancet 1988;1:197–203.
70. The TIMI Research Group. Immediate vs. delayed catheterization and angioplasty following thrombolytic therapy for acute myocardial infarction: TIMI II A results. JAMA 1988;260:2849–58.
71. Detre K, Holubov R, Kelsey S, et al. Percutaneous transluminal coronary angioplasty in 1985–1986 and 1977–1981: the National Heart, Lung, and Blood Institute Registry. N Engl J Med 1988;318:265–70.
72. Ellis SG, O'Neill WW, Bates ER, et al. Implications for patient triage from survival and left ventricular functional recovery analyses in 500 patients treated with coronary angioplasty for acute myocardial infarction. J Am Coll Cardiol 1989;13:1251–9.
73. Mundth ED, Buckley MJ, Leinbach RC, Gold HK, Daggett WM, Austen WG. Surgical intervention for the complications of acute myocardial ischemia. Ann Surg 1973;178:379–88.
74. Miller MG, Weintraub RM, Hedley-Whyte J, Restall DS, Alexander M. Surgery for cardiogenic shock. Lancet 1974;2:1342–5.
75. Willerson JT, Curry GC, Watson JT, et al. Intra-aortic balloon counterpulsation in patients in cardiogenic shock, medically refractory left ventricular failure and/or recurrent ventricular tachycardia. Am J Med 1975;58:183–91.
76. Johnson SA, Scanlon PJ, Loeb HS, Moran JM, Pifarre R, Gunnar RM. Treatment of cardiogenic shock in myocardial infarction by intra-aortic balloon counterpulsation and surgery. Am J Med 1977;62:687–92.
77. Ehrich DA, Biddle TL, Kronenberg MW, Yu PN. The hemodynamic response to intra-aortic balloon counterpulsation in patients with cardiogenic shock complicating acute myocardial infarction. Am Heart J 1977;93:274–9.
78. Bardet J, Masquet C, Kahn JC, et al. Clinical and hemodynamic results of intra-aortic balloon counterpulsation and surgery for cardiogenic shock. Am Heart J 1977;93:280–8.
79. O'Rourke MF, Sammel N, Chang VP. Arterial counterpulsation in severe refractory heart failure complicating acute myocardial infarction. Br Heart J 1979;41:308–16.
80. Subramanian VA, Roberts AJ, Zema MJ, et al. Cardiogenic shock following acute myocardial infarction: late functional results after emergency cardiac surgery. NY State J Med 1980;80:947–52.
81. DeWood MA, Notske RN, Hensley GR, et al. Intraaortic balloon counterpulsation with and without reperfusion for myocardial infarction shock. Circulation 1980;61:1105–12.
82. Kirklin JK, Blackstone EH, Zorn GL Jr, et al. Intermediate-term results of coronary artery bypass grafting for acute myocardial infarction. Circulation 1985;72(suppl II):II-175–8.
83. Phillips SJ, Zeff RH, Skinner JR, Toon RS, Grignon A, Kongtahworn C. Reperfusion protocol and results in 738 patients with evolving myocardial infarction. Ann Thorac Surg 1986;41:119–25.
84. Laks H, Rosenkranz E, Buckberg GD. Surgical treatment of cardiogenic shock after myocardial infarction. Circulation 1986;74(suppl III):III-11–6.
85. Guyton RA, Arcidi JM Jr, Langford DA, et al. Emergency coronary bypass for cardiogenic shock. Circulation 1987;76(suppl V):V-22–7.

86. Bolooki H. Emergency cardiac procedures in patients in cardiogenic shock due to complications of coronary artery disease. Circulation 1989;79(suppl I):I-137–48.
87. Ohman EM, Califf RM, George BS, et al. The use of intraaortic balloon pumping as an adjunct to reperfusion therapy in acute myocardial infarction. Am Heart J 1991;121:895–901.
88. Shawl FA, Domanski MJ, Punja S, Hernandez TJ. Emergency percutaneous cardiopulmonary (bypass) support in cardiogenic shock (abstr). J Am Coll Cardiol 1989;13:160A.
89. Jacobs AK, Faxon DP. Reperfusion and PTCA. In: Topol EJ, ed. Textbook of Interventional Cardiology. Philadelphia: WB Saunders, 1990:477–95.
90. Lincoff AM, Popma JJ, Bates ER, et al. Successful coronary angioplasty in two patients with cardiogenic shock using the Nimbus Hemopump support device. Am Heart J 1990;120:970–2.
91. Neuhaus K-L, Feurer W, Jeep-Tebbe S, Niederer W, Vogt A, Tebbe U. Improved thrombolysis with a modified dose regimen of recombinant tissue-type plasminogen activator. J Am Coll Cardiol 1989;14:1566–9.
92. Topol EJ, Califf RM, George BS, et al. Coronary arterial thrombolysis with combined infusion of recombinant tissue-type plasminogen activator and urokinase in patients with acute myocardial infarction. Circulation 1988;77:1100–7.
93. Califf RM, Topol EJ, Stack RS, et al. Evaluation of combination thrombolytic therapy and timing of cardiac catheterization in acute myocardial infarction: results of Thrombolysis and Angioplasty in Myocardial Infarction Phase 5 randomized trial. Circulation 1991;83:1543–56.